paper, it would appear to be most efficiently considered along with the pending claims. Claims 63, 72, 74, 78, 80, 82 and 94-97 are cancelled without prejudice pursuant to the Examiner's restriction requirement and Applicants' election of invention. The amendment to the claims has been made to place the application in condition for allowance in order to expedite issuance of a patent directed to the claimed subject matter. The claims are directed to a method for eliciting an immune reaction in a prospective mother to an antigen or antigens of a prospective father in order to alleviat the symptoms of infertility using TGFβ in combination with the father's antigens. The method results in the alleviation of infertility by allowing the mother to toleratc the father's antigens, which would otherwise complicate fertility. Support for the amendment to the claims can be found throughout the originally filed specification and claims and in particular, in the examples which appear on pages 21-29. No new matter is believed to have been added by way of this amendment. Applicants respectfully submit that the instant claims are now in condition for allowance.

The Examiner has objected to and/or rejection the specification and/or the claims of the originally filed application under 35 U.S.C. §§112, first and second paragraphs as well as 103. Applicants have either addressed the Examiner's concerns such that they have been motted by virtue of the instant amendment or are respectfully traversed for the reasons which are presented in the following sections.

The Objection to the Specification

The Examiner raises a number of well-founded objections to the specifications which are specified in the office action on page 3. Applicants have endeavored to address the Examiner's rejections by amending the specification accordingly. Applicants have amended the specification to reflect priority from the corresponding PCT appliction PCT/AU9800149. Applicants have also amended the specification to correct typos contained therein as well as provided an Abstract of the disclosure. With respect to the drawings/figures, substitute formal drawings will be

submitted at the appropriate time prior to or at payment of the issue fee.

The §112, First Paragraph Rejection

The Examiner has rejected the originally filed claims under 35 U.S.C. §112, first paragraph as failing to enable certain claimed embodiments. In order to address the Examiner's rejection, Applicants have deleted from the claims any reference to "derivative or analog thereof". Note that Applicants have maintained their position that the use of TGFβ_1, β_2 and B_3 are clearly enabled by the teachings of the specification. It is respectfully submitted that the teachings of the specification with respect to the use of TGFβ_1, which the Examiner readily agrees supports the enablement of the claims with respect to that isotype, also support enablement for the closely related isotypes of TGFβ_2 and TGFβ_3. Applicants accordingly have deleted reference in the claims to "derivatives and analogs of TGF", but have maintained reference to isotypes of TGF which, because of their closely related structures to TGFβ_1 (see the specification at page 6, lines 11-24), are fully expected to be useful and to work in the present invention. Moreover, to the extent that the Examiner accepts the enablement of the instant application with respect to TGFβ_1, modification of the present teachings can only be seen as routine when using isotypes TGFβ_2 or TGFβ_3 for essentially the same purposes as TGFβ_1.

It is respectfully submitted that the amended claims are enabled and are in compliance with the requirements of 35 U.S.C. §112, first paragraph.

The §112, Second Paragraph Rejection

The Examiner has rejected the pending claims under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. In order to address the Examiner's rejection, Applicants have deleted the term "derivative or analog thereof" from the claims, thus obviating the Examiner's rejection in this regard. In addition, Applicants have amended claim 65 to be dependant on claim 51, not 50, as in the case of claim 64, thus obviating the Examiner's rejection of these two claims that they are identical.

The §103 Rejection

Turning to the Examiner's §103 rejection, the Examiner had rejected the original claims as being obvious over Feinberg, et al., U.S. patent no. 5,395,825 ("Feinberg"), in view of Gafter, et al., J. Clinical Immun., 17(5): 407-419, 1997 ("Gafter"). The Examiner cites Feinberg for teaching a method of treating infertility by administering TGFβ, wherein the TGFβ can be $TGF\beta_2$, to a female to increase the success rate of implantation. The Examiner argues that Feinberg teaches that the $TGF\beta_2$ may be administered before, after or simultaneously with male antigens, including sperm of the prospective father and antigens from the conceptus to the mucosal surface.

The Examiner cites Gafter for teaching a method of treating infertility by immunizing the female with one or more paternal leukocyte antigens prior to conception and that TGFβ is an effective analog of $TGF\beta_2$. In addition, the Examiner cites Gafter for teaching that an increase of TGFβ would lead to immune modulation/suppression of cell-mediated immune responsses of the female host and immune tolerance toward the conceptus and maintenance of pregnancy.

Based upon these two disclosures, the Examiner argues that it would have been *prima*

facie obvious to combine the teachings of Feinberg and Gafter to produce the presently claimed methods. Applicants respectfully traverse the Examiner's rejection.

The present method is directed to eliciting an immune reaction in a prospective mother to one or more antigens of a prospective father to alleviate symptoms of an infertility condition, the method comprising exposing the prospective mother to one or more paternal antigens in combination with TGFβ, the method leading to tolerance to the paternal antigens and allevation of the symptoms of the infertility condition. It is respectfully submitted that the claimed invention is not *obvious* over the cited disclosures.

In the first instance, Gafter is not prior art to the present invention, inasmuch as Gafter has a date of acceptance of May 1, 1997, several months after the priority date of the present application (priority based upon Australian application PO 5508, having a priority date of 6 March 1997). It is noted that when a publication is accepted, it is often *several months* before the article is actually published. Thus, Gafter has a publication date which is long after the filing date of the priority Australian application upon which priority of the instant application is based. Therefore, it is respectfully submitted that Gafter is not prior art to the instant application.

Turning to Feingberg, it is respectfully submitted that Feinberg does not disclose or suggest the present invention. There is a very clear distinction between the instant invention and the disclosure of Feinberg. Whereas, the present invention relates to the induction of tolerance as a method of assisting with or treating fertility conditions, in contrast, Feinberg relates to the stimulation of the production of trophoblast fibronectin to assist with implantation of the conceptus.

It turns out that the effector molecule used in the present invention and in the disclosed method of Feinberg is the same, namely TGFβ, and that both inventions address a problem which is in the same general field, namely fertility. However, the pathway to achieving the result

in each of the two methods is completely different and the effect is different. The induction of tolerance in the case of the instant invention has ramifications from conception at day 1 through well into pregnancy that are related to adverse immunological reactions by the prospective mother which can give rise to a result ranging from total rejection of the conceptus/embryo through to more mild reactions. In the case of Feinberg, implantation is enhanced by inducing fibronectin production, which has benefit solely for implantation (which in humans occurs at day 4) and plays no role in alleviating adverse immunological reactions. Feinberg does not mention immune tolerance or any immunological mechanism, simply because it is not even relevant to the benefit he has found, i.e., increased adherence.

Different regimes are used on the one hand to induce fibronectin production when compared to inducing tolerance. We have previously pointed to the timing of the administration of TGFβ for tolerance when compared to induction of fibronectin induction, given the half life of TGFβ. The Feinberg invention requires the stimulation of fibronectin production to have an effect that is coincident with a very short window, i.e., day 4 after conception. A second and even more substantial difference in the regimes of administering TGFβ is the quantity required to induce tolerance. In particular, Feinberg alludes to concentrations of TGFβ which are well below those which are demonstrated by the present inventors to elicit responses.

In column 6, lines 33 to 41 of Feinberg, the concentrations are represented in the following terms:

> Transforming growth factor β is typically administered in doses of about 0.1 ng/ml to about 10ng/ml. Preferably from about 0.5 ng/ml to about 5 ng/ml is administered. Still more preferably, from about 1 ng/ml to about 3 ng/ml of TGFβ is administered, the concentrations referring to the fluid in which the conceptus is suspended. In other preferred embodiments of the present invention from about 1.5 ng/ml to about 2.5 ng/ml TGFb are administered to a conceptus.

In Example 6 of Feinberg, which looks at the attachment of trophoblasts to plasma fibronectin surfaces, TGFβ was used at a final concentration of 1 ng/ml (see column 10, line 38 of Feinberg).

In contrast, as presented in Example 6, the present invention requires that at least 10 ng of TGFβ is required per mouse uterus to show an effect, the 10 ng is delivered at a concentration of 200 ng/ml. Where 2 ng is delivered per uterus (the equivalent of 40 ng/ml), no effect is shown.

Similarly, referring to Table 1 on page 22, the levels of TGFβ used were 400ng/ml, which is a level at which reliable results can be obtained. Of course, this level will obviously vary as a function of the species concerned, but the levels found by the present inventors to induce a tolerance effect is in fact *2 orders of magnitude higher than that used by Feinberg*, and over 1 order ot magnitude greater than the very highest level contemplated by Feinberg.

Accordingly, it is clear that the use of the method disclosed in Feinberg will not provide tolerance or the benefits which accrue from tolerance, for example, elevating the levels of TGFβ used. Accordingly, the instant invention cannot be fairly said to be disclosed or suggested by the teachings of Feinberg.

For the above reasons, Applicant respectfully asserts that the claims set forth in the present amendment are now in compliance with 35 U.S.C. Applicant respectfully submits that the present application is now in condition for allowance and such action is earnestly solicited.

Applicant has cancelled 10 claims (dependent) and added no claims. No fee is believed due for the presentation of this amendment. Please credit any overpayment or charge any fee due to Deposit Account No. 04-0838. A petition establishing small entity status is on file in this application. An appendix evidencing the amendments to the claims and specification is attached hereto.

Dated: 6/14/01

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being sent by facsimile transmission to Examiner P.Huynh in the United States Patent Office, Group Art Unit 1644 on June 14, 2001.

_____
Henry D. Coleman (Reg. No. 32,559)

Appendix

Amendments

In the Specification:

At page 1, after the title of the application, please insert the following:

--Related Applications
This application is a §371 filing of PCT/AU98/00149 (WO 98/39021), filed 3/6/98.--

On page 7, line 7, change "antigen" to --antigens--.

On page 15, line 22, change "presence of absence" to --presence or absence--.

On page 21, line 4, change "37oC" to --37°C--.

Please insert the following paragraph on a separate page after the claims:

In the Abstract
The following abstract should be inserted at the end of the specification (claims):

ABSTRACT

A method of treating an infertility condiiton in humans or mammals, by exposure of a prosective mother to TGFβ . The exposure is advantageously in conjunction with one or more antigens of a prospective father so that a hyporesponsive immune reaction is mounted to the one or more antigens of the prospective father.

In the Claims:

Please amend the claims as follows:

50. A method of [treating an infertility condition in a human or mammal by exposure of] eliciting an immune reaction in a prospective mammalian mother to one or more antigens of a prospective father to allcviate symptoms of an infertility conditions, said method comprising

exposing said prospective mother to said one or more antigens of said prospective father and to substantially purified TGFβ[or an effective derivative or analog thereof before attempted conception to elicit an immune reaction leading], said method leading to tolerance to said one or more antigens [to thereby alleviate] and alleviation of symptoms of the infertility condition.

51. (Amended) The method according to [A method of treating an infertility condition as in] claim 50] wherein a mucosal surface of the prospective mother is exposed to one or more antigens.

52. (Amended) The method according to [A method of treating an infertility condition as in] claim 51 wherein the mucosal surface is selected from the group comprising an oral mucosal surface, a respiratory mucosal surface, a gastrointestinal mucosal surface or a genital mucosal surface.

53. (Amended) The method according to [A method of treating an infertility condition as in] claim 51 wherein the mucosal surface is a genital mucosal surface.

54. (Amended) The method according to[A method of treating an infertility condition as in] claim 51 wherein the one or more antigens and TGFβ [or derivative or analog thereof] is injected for systemic contact.

55. (Amended) The method according to [A method of treating an infertility condition as in] claim 51 wherein the TGFβ [or derivative or analog thereof] and the one or more antigens are administered at one site.

56. (Amended) The method according to [A method of treating an infertility condition as in] claim 51 wherein the TGFβ [or derivative or analog thereof] and the one or more antigens are each administered at a first site and a different site respectively.

57. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the TGFβ [or derivative or analog thereof] and the one or more antigen are administered temporarily spaced apart.

58. (Amended) The method according to[A method of treating an infertility condition as in] claim 57 wherein the one or more antigens are administered subsequent to an administration of the TGFβ [or derivative or analog thereof].

59. (Amended) The method according to [A method of treating an infertility condition as in] claim 57 wherein the one or more antigens are administered first followed by administration of TGFβ [or derivative or analog thereof].

60. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the one or more antigens are chosen as a result of being particularly antigenic and prominent either on the sperm, or on the conceptus.

61. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the one or more antigens are present on cells taken from the prospective father that contain MHC antigens.

62. (Amended) The method according to [A method of treating an infertility condition as in] claim 61 wherein the antigen is an MHC I antigen of the prospective father.

63. Cancelled.

64. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the one or more antigens are administered on sperm cells of the prospective

father.

65. (Amended) The method according to [A method of treating an infertility condition as in] claim [50] 51 wherein the one or more antigens are administered on sperm cells of the prospective father.

66. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the one or more antigens are presented in purified or semi-purified form.

67. (Amended) The method according to [A method of treating an infertility condition as in] claim 66 wherein the purified or semi-purified onc or more antigens are presented on inert or adjuvant carriers.

68. (Amended) The method according to [A method of treating an infertility condition as in] claim 51 wherein humans are being treated, and the exposure of TGFβ is to a mucosal surface and the level of TGFβ is greater than 50 ng/mL with a total dose of 150 ng/mL.

69. (Amended) The method according to [A method of treating an infertility condition as in] claim 51 wherein the mucosal surface is exposed to a concentration of TGFβ of between 100 and 400 ng/mL with a total dose of between 100 to 2000 ng.

70. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the TGFβ [or derivative or analog thereof] is supplied in a slow release form.

71. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the exposure of the one or more antigens is to the prospective mother's genital tract in the form of the prospective father's ejaculate, and the level of exposure is

determined by the cell count and antigenic density on the surface of such cells.

72. Cancelled.

73. A method of treating an infertility condition as in claim 50 wherein the TGFβ is selected from the group consisting of $TGF\beta_1$, $TGF\beta_2$ and $TGF\beta_3$.

74. Cancelled.

75. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the TGFβ is modified.

76. (Amended) The method according to [A method of treating an infertility condition as in] claim 75 wherein the modification [is selected from the group comprising] comprises substitution, deletion or addition mutants[,] or peptide fragments of TGFβ [or derivative or analog thereof, and peptide fragments of TGFβ or derivative or analog thereof which have been incorporated into another protein].

77. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the TGFβ [or derivative or analog thereof] is a member of the TGFβ superfamily.

78. Cancelled.

79. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein TGFβ is administered in its active form.

80. Cancelled.

81. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the prospective mother is incapable of converting sufficient of the inactive form of TGFβ to active TGFβ , and the method of treating includes administration of active TGFβ.

82. Cancelled.

83. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the prospective mother is incapable of converting the inactive form of TGFβ to active TGFβ, and the method of treating includes administration of plasmin, so as to increase the level of active TGFβ.

84. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein TGFβ is administered in an unpurified form using a biological source rich in TGFβ.

85. (Amended) The method according to [A method of treating an infertility condition as in] claim 84 wherein the TGFβ is administered in the form of platelets.

86. (Amended) The method according to [A method of treating an infertility condition as in] claim 51 wherein humans are being treated and the exposure to TGFβ and male antigen is a multiple exposure.

87. (Amended) The method according to [A method of treating an infertility condition as in] claim 86 wherein the multiple exposure is preferably performed over a period spanning at least three months prior to attempted conception.

88. (Amended) The method according to [A method of treating an infertility condition as

in] claim 50 wherein humans are being treated and exposure is at least one week before conception is attempted.

89. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein the exposure is before attempted conception.

90. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 wherein administration of TGFβ [or derivative or analog thereof] and the one or more antigen occurs at least once after the prospective date of conception.

91. (Amended) The method according to [A method of treating an infertility condition as in] claim 90 wherein the exposure continues over a period of the first 12 weeks of pregnancy.

92. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 first including the step of diagnosing or testing whether the male has adequate levels of TGFβ or the female has the capacity to activate TGFβ, or alternatively whether anti-sperm antibodies exist.

93. (Amended) The method according to [A method of treating an infertility condition as in] claim 50 used in conjunction with IVF treatment, whereby the transient hyporeactive immune response is elicited before transfer of the conceptus or gametes is attempted.

94. Cancelled.

95. Cancelled.

96. Cancelled.